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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,734	10/31/2005	Timothy S. Gardner	0079571-0141	7041

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EXAMINER	
RIGGS II, LARRY D	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
08/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/506,734	GARDNER ET AL.	
	Examiner	Art Unit	
	LARRY D. RIGGS II	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-65,77,84 and 86-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-65,77,84 and 86-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed 6/7/2010 are acknowledged and entered.

Status of Claims

Claims 1-58, 66-76, 78-83 and 85 are cancelled. Claims 59-65, 77, 84 and 86-94 are currently pending and examined on the merits.

Withdrawn Rejections/Objections

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn in view of the amendments filed 6/7/2010. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statements filed 6/7/2010 is acknowledged. A signed copy of the corresponding 1449 form has been included with this Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59-63, 77, 84 and 86-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoughton et al. (US 6,132,969) (IDS filed 10/6/06) in view of Marnellos et al. (IDS filed 6/7/2010) in view of Ideker et al. (Science, 2001, 292, 929-934) in view of Lew et al. (J. Clin. Invest., 1991, 87, 100-112).

The instant claims are drawn to a method of identifying a target of a perturbation comprising the steps of (a) perturbing a biological system comprising a plurality of biological species, (b) characterizing a response by

determining quantitative changes of expression activity of the biological species at steady state; (c) calculating predicted perturbations to individual species that would yield the same response characterized in step (b) using a programmed computer using a pre-determined quantitative model of the biological system, wherein the predictions are calculated based on changes of expression or activity of individual species; and (d) identifying an individual species as a target of the perturbation when the predicted perturbation meets a predefined criterion.

Regarding claims 59, 77 and 84, Stoughton et al. teaches a biological network of cellular constituents and network models suitable for expressing changes observed in the cellular constituents during experiments on a biological system, predictions of changes in cellular constituents according to a network model and assessment of the goodness of fit of a prediction to experimental results as suitably expressed, (column 6, last paragraph – column 7, first paragraph; Figure 1). Stoughton et al. teaches a perturbation in the form of compounds (drugs), (column 7, last paragraph; column 11, lines 1-9; column 43, lines 30-62). Stoughton et al. teaches predictions of sets of outputs of the same response type, classes 1, 2, and 3, represents redirection of protein for the drug tacrolimus and output classes 5,6, and 7 that represent redirection of protein cph by the drug cyclosporine A (column 11, lines 3-13). Stoughton et al. shows computer systems, including memory with software and processors, for carrying out the computational steps of the method, (abstract; column 54-56; Figures 12 and 13).

While Stoughton teaches that multiple intermediate states may be used by continuous control of gene and protein functions, to predict a change at the output to inform the connectivity of the biological network, (column 8, line 53-column 9, line 60), Stoughton does not specifically teach characterizing a response by determining quantitative changes of expression or activity with a pre-determined quantitative model. Stoughton et al. does not teach allowing the biological network to reach a steady state. While Stoughton et al. teaches classes of constituents that provide the same response to a perturbation, i.e. redirection of a protein, Stoughton et al. do not teach identifying particular cellular constituents of a particular model output class (species).

Marnellos et al. teaches a pre-determined quantitative model that predicts changes in cellular constituents (species) by analysis of regulatory gene interaction and known patterns of gene expression datasets, wherein optimization of parameters in the model are to fit schematic gene expression datasets and allow solutions with respect to system perturbations, (page 38, second paragraph – page 40, third paragraph).

Stoughton et al. and Marnellos et al. do not teach identifying particular cellular constituents of a particular model output class (species) or allowing the biological network to reach a steady state.

Ideker et al. builds, test and refines a model of a cellular pathway in which perturbations to critical pathway components are analyzed to identify 997 messenger RNAs responding to 20 systematic perturbations of the yeast

galactose-utilization pathway, (abstract; page 930, right column; Figures 1-5). The set of 997 genes was divided into 16 clusters where each cluster contained genes with similar expression responses over all perturbations, (page 931, left column, first paragraph; page 933, left column – middle column; Figures 2-5).

Stoughton et al., Marnellos et al. and Ideker et al. do not teach allowing the biological network to reach a steady state.

Lew et al. shows a mathematical model of volume, pH and ion current regulation in reticulocytes, (abstract). Lew et al. shows a model of a pH dependence of the K:Cl cotransport and Na pathways, that result in new steady state from the original reference state following transient perturbations, (page 103, right column, last paragraph – page 105, left column, first full paragraph; Figures 1, 2, 5, 6 and 9).

Regarding claim 60, Stoughton et al. shows targeting a protein with a drug (small molecule) known to interact with the targeted protein, (43, lines 30-62).

Regarding claims 61-63, Stoughton et al. shows statistical tests of the significance of the goodness of the overall fit found for the network model, (column 10, lines 31-40; column 23, line 37 – column 26, line 50). Stoughton et al. shows a cellular constituent can be assigned to the greatest output class where a threshold can be set for the sum of constituents, (column 22- line 52 – column 23, line 20).

Regarding claim 86, Marnellos et al. teaches a model that quantifies the dynamics of gene expression in individual cells, (abstract; page 40, first paragraph).

Regarding claims 87 and 88, Stoughton et al. teaches an influence matrix that predicts a behavior output of an element in response to an experiment that can vary on the level of abstraction of the model, (column 19, lines 15-24; column 21, line 33 – column 22), and determining a magnitude of the perturbation through calculation of the ratio of the emission of fluorophores in an assay, (column 51, lines 28-36; Equation 2, Section 5.2), which reads on a measure of sensitivity of the activity of a species. Stoughton et al. teaches that more weight is put on larger values of the measures of change of a cellular constituent when the fit values for all genes are combined to an over-all fit value, (column 23, lines 33-36), which reads on the strength of influence exerted by a species on a species.

Regarding claim 89, Marnellos et al. teaches resolving novel cell clusters with respect to perturbations, (page 38, penultimate paragraph; Figure 2).

Regarding claims 90 and 91, Stoughton et al. teaches species are genes, (column 13, lines 14-67; Figures 4 and 5).

Regarding claim 92, Stoughton et al. teaches measuring mRNA in response to a perturbation, (column 31, lines 47-59). Stoughton et al. teaches quantitative monitoring of gene expression patterns with cDNA microarray, (column 46, lines 28-40).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of testing biological network models of Stoughton et al. with the quantitative modeling by Marnellos et al., the identification of mRNAs with integrated genomic and proteomic analysis of a perturbed network by Ideker et al. and allowing the biological network to reach a steady state after perturbation as in Lew et al. because Marnellos et al. teaches that predictions based on quantitative gene expression allow the study of dynamics of cell cluster resolution and interactions over time and dynamics of gene expression in individual cells, (abstract; page 38, second and third paragraphs), Ideker et al. teaches that the integration of mRNA and protein expression measurements must be integrated for an understanding of biological systems, (page 931, left column, last paragraph) and because Lew et al. shows that a steady-state different from the original steady-state may result from perturbations of a network, (page 103, right column, last paragraph – page 104, left column, first paragraph).

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Stoughton et al. (US 6,132,969) (IDS filed 10/6/06) in view of Marnellos et al. (IDS filed 6/7/2010) in view of Ideker et al. (Science, 2001, 292, 929-934) in view of Lew et al. (J. Clin. Invest., 1991, 87, 100-112) as applied to claims 59-63, 77, 84 and 86-92 above, and further in view of Wannenburg et al., (Am. J. Physiol. Heart Cir. Physiol., 2000, 279, H779-H790).

The instant claim 64 depends from claim 59 with the extra limitation wherein a predicted perturbation is identified as statically significant using a statistical test from the group consisting of z-test, t-test and chi-squared test.

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. are applied to claims 59-63, 77, 84 and 86-92 above.

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. do not show a statistical test from the group consisting of z-test, t-test and chi-squared test.

Wannenburg et al. shows the effect of calcium activation on characteristic frequency parameters using statistical tests, in individual rat cardiac trabeculae, (abstract; page H785, left column, second paragraph; Figure 4; Table 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of testing biological network models of Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. with the confirmation of a significant perturbation via a statistical test by Wannenburg et al. because Wannenburg et al. shows that statistical tests, e.g. t-test help determine which parameter in a system may be significantly perturbed with respect to other parameters in that system, e.g. b and c characteristic frequencies, (page H785, left column, second paragraph; Figure 4; Table 2).

Claims 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stoughton et al. (US 6,132,969) (IDS filed 10/6/06) in view of Marnellos et al. (IDS filed 6/7/2010) in view of Ideker et al. (Science, 2001, 292, 929-934) in view

of Lew et al. (J. Clin. Invest., 1991, 87, 100-112) as applied to claims 59-63, 77, 84 and 86-92 above, and further in view of Scheidt et al., (J. Neurophysiol. 2001, 86, 971-985).

The instant claim 65 depends from claim 59 with the extra limitation the statistical test is used with estimates of moments of the probability density functions of the predicted perturbations.

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. are applied to claims 59-63, 77, 84 and 86-92 above.

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. do not show the statistical test is used with estimates of moments of the probability density functions of the predicted perturbations.

Scheidt et al. shows Gaussian and bimodal probability density functions of perturbation sequence trials, (Figure 2), wherein a t-test determined that the unimodal and bimodal experiments were not significantly different, (page 981, right column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of testing biological network models of Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. with the probability density function and a statistical test by Scheidt et al. because Scheidt et al. shows that probability density function distribution of moments combined with a statistical test, e.g. t-test, help determine whether a probability density is significant (page 981, right column, last paragraph), and one skilled in the art

would recognize that moments of probability distribution function about responses of biochemical species and response of values of perturbations would better determine the significance of a perturbation of a particular biochemical species when assessed by a statistical test, e.g. t-test.

Claims 93 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stoughton et al. (US 6,132,969) (IDS filed 10/6/06) in view of Marnellos et al. (IDS filed 6/7/2010) in view of Ideker et al. (Science, 2001, 292, 929-934) in view of Lew et al. (J. Clin. Invest., 1991, 87, 100-112) as applied to claims 59-63, 77, 84 and 86-92 above, and further in view of Steuerwald et al., (Molecular Human Reproduction, 2000, 6(5), 448-453).

The instant claims 93 and 94 depend from claim 59 with the extra limitations wherein quantitative changes of mRNA levels are measured by real-time PCR (claim 93), and the predicted changes are changes of mRNA levels, (claim 94).

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. are applied to claims 59-63, 77, 84 and 86-92 above.

Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. do not teach quantitative changes of mRNA levels are measured by real-time PCR or predicted changes of mRNA levels.

Steuerwald et al. teaches quantification of mRNA by real-time PCR, (abstract; page 449, left column, first and second paragraphs). Marnellos et al. teaches the predictions of the dynamics of gene expression in individual cells, by

predicting the concentration of the product of a gene, (abstract; page 32, first paragraph; Equation 2), suggesting that mRNA levels can be predicted.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of testing biological network models of Stoughton et al., Marnellos et al., Ideker et al. and Lew et al. with the quantification of mRNA in real-time with PCR by Steuerwald et al. because Steuerwald et al. shows the highly sensitive technique used allows the monitoring of log-linear phase amplification during which the most useful quantitative data is obtained, (abstract), and one skilled in the art would recognize that the most useful quantitative data would better determine the significance of a perturbation of a particular biochemical species and a calculation of a predicted perturbation.

Response to Arguments

Applicant's arguments filed 6/7/2010 have been fully considered but they are not persuasive.

Applicants argue that all limitations of the instant claims are not met by the cited art. Applicants argue that the cited art does not use a quantitative model to predict quantitative changes of expression or activity of individual species that would yield the same response by the perturbation.

Applicants' arguments are moot in light of the newly cited art of Marnellos et al. and Ideker et al. which teaches a quantitative model that predicts quantitative changes of expression or activity of individual species, (Marnellos et al., page 38, second paragraph – page 40, third paragraph), and identification of

genes that respond similarly to perturbations, (Ideker et al., page 931, left column, first paragraph). All limitations of the instant claims are met by the cited art above.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LDR/
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